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14. ABSTRACT

Individuals with germline mutations in BRCA1 have an elevated but incomplete risk of developing ovarian cancer suggesting the presence of genetic modifiers of ovarian cancer in this population. A genome wide association study (GWAS) for ovarian cancer in BRCA1 mutation carriers was initiated in an effort to identify common genetic variants that modify ovarian cancer risk. Discovery and validation studies have identified several novel modifiers of ovarian cancer risk for BRCA1 mutation carriers that can be used for individualized ovarian cancer risk assessment.

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BRCA1, ovarian cancer, genome wide association study, association study

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Introduction:

Inactivating mutations in the *BRCA1* tumor suppressor gene have been detected in approximately 10% of all ovarian cancers. Individuals with germline mutations in *BRCA1* have a substantially increased risk of developing ovarian cancer as compared to the general population, with an estimated cumulative risk of ovarian cancer by age 70 of 39% [1]. These findings indicate that although *BRCA1* mutation carriers are at high risk for developing ovarian cancer, a sizeable proportion of women who carry a deleterious mutation will not develop this disease. In addition, the findings show that there is considerable variation in the age of onset of ovarian cancer in this population. This variable penetrance and age of onset of ovarian cancer suggest that there are additional genetic and environmental factors that modify the age specific risk of ovarian cancer for *BRCA1* mutation carriers. Common genetic variants that are associated with the risk of ovarian cancer have recently been identified through candidate gene and genome wide association studies in the general population [2-4]. This suggests that common genetic variants may also modify ovarian cancer risk in carriers of *BRCA1* mutations. Identification of these genetic risk factors may prove useful for identifying those *BRCA1* carriers at elevated or lowered risk of ovarian cancer compared to the average *BRCA1* carrier. Women at increased risk may subsequently benefit from enhanced screening or certain prevention measures such as prophylactic oophorectomy, whereas women at lowered risk may be able to avoid these types of intervention [5]. Thus, we proposed a study aimed at identifying genetic risk factors for ovarian cancer in BRCA1 mutation carriers through a genome wide association study in BRCA1 mutation carriers. The overall intent was to complete a genome wide association study of *BRCA1* carriers, validate candidate risk modifiers, to assess the contribution of these modifiers to sporadic ovarian cancer and to develop risk prediction models.

Body

Aim 1: To conduct a genome-wide association scan in 1,000 *BRCA1* carriers with ovarian cancer and 1,000 age-matched unaffected *BRCA1* carriers.

As outlined in detail in our previous annual report, we recently conducted a GWAS of 1250 *BRCA1* mutation carriers diagnosed with breast cancer and 1250 unaffected *BRCA1* carriers using Human660W-Quad arrays. The 1250 unaffected included 361 diagnosed with ovarian cancer. Subsequently we collected and genotyped an additional 434 *BRCA1* mutation carriers diagnosed with ovarian cancer on Human660W-Quad arrays. In addition we acquired GWAS genotype data for 120 additional *BRCA1* mutation carriers affected with ovarian cancer from collaborators. Together this resulted in GWAS genotype data from 915 *BRCA1* mutation carriers diagnosed with ovarian cancer. Final analyses of genotyping data included 897 *BRCA1* mutation carriers with ovarian cancer and approximately 540,000 SNPs. In collaboration with Drs. Douglas Easton and Antonis Antoniou at the University of Cambridge, we evaluated associations with both breast and ovarian cancer using a retrospective likelihood model. This accounts for the age extremes of affected and unaffected and also applies age related penetrance estimates for *BRCA1* carriers. Carriers were censored at age of onset of disease for those affected with breast or ovarian cancer and age of last follow up or age at prophylactic mastectomy/oophorectomy for those with no cancer diagnosis. Analyses were adjusted for Country of origin because samples from 26 different centers in 18 countries were included in the study. For ovarian cancer, 10 SNPs exhibited associations of $p<1 \times 10^{-5}$ and 37 had associations of $p<1 \times 10^{-4}$. Interestingly, rs1339552 on chromosome 9 in BCN2 and rs7651446 from TIPARP on chromosome 3 found to exhibit genome wide associations with ovarian cancer in the general population also showed highly significant associations ($p=1.9 \times 10^{-5}$ and $p=1.7 \times 10^{-4}$, respectively) with ovarian cancer in *BRCA1* mutation carriers. These loci can be considered genetic risk factors for ovarian cancer in *BRCA1* mutation carriers.

These efforts completed the proposed studies in Aim, which include Task 1-4.

Aim 2: To further evaluate observed associations between ovarian cancer risk and SNPs implicated in Aim 1 by genotyping 1,500 *BRCA1* ovarian cancer cases and 1,500 unaffected *BRCA1* carriers.

Validation of Chromosome 19p13.1 associations

We previously reported that variants from the 19p13.1 locus were associated with ovarian cancer risk in a genotyping study of 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers, which included 1,465 *BRCA1* mutation carriers and 453 *BRCA2* mutation carriers with ovarian cancer. We used a competing risk analysis that accounted for the effects on breast and ovarian cancer in parallel. In this competing risk analysis rs67397200 at 19p13.1 was strongly associated with ovarian cancer risk in *BRCA1* (HR=1.16; 95%CI 1.05-1.29; $p=3.8x10^{-4}$) and *BRCA2* (HR=1.30; 95%CI 1.10-1.52; $p=1.8x10^{-3}$) mutation carriers. This SNP and others in this locus were also associated with breast cancer risk in *BRCA1* mutation carriers. These are the first variants found to influence both breast and ovarian cancer risk in either *BRCA1* or *BRCA2* mutation carriers.

GWAS validation studies

The original intent for this project was to further evaluate the 384 most significantly associated SNPs from the *BRCA1* ovarian cancer GWAS in 3,000 additional *BRCA1* mutation carriers including 1,500 with ovarian cancer. However, in 2010 we were provided the opportunity to participate in a large multi-consortium replication study. Specifically, we designed a SNP array (iCOGS) containing 211,000 candidate SNPs from GWAS of various tumor types. A total of 35,000 candidate SNPs were selected from the *BRCA1* GWAS including 6,000 from the *BRCA1* Ovarian Cancer GWAS. Testing of the arrays showed that 204,000 of the SNPs yielded good quality genotyping.

Analyses of associations with ovarian cancer risk for 8,054 unaffected and 1,264 affected *BRCA1* carriers (Stage 2) revealed no evidence of inflation in the association test-statistic (λ=1.039, adjusted to 1000/1000 cases/controls λ=1.018). When combined with the original GWAS data (stage 1 samples) for a total of 9866 unaffected and 1839 affected with ovarian cancer, 62 SNPs in 17 regions were associated with ovarian cancer risk for *BRCA1* carriers at $P<10^{-4}$. These included SNPs in the BNC2 9p22 and 3q25 loci previously associated with ovarian cancer risk in both the general population and *BRCA1* carriers. Associations (P<0.01) with ovarian cancer risk were also observed for SNPs in three other known ovarian cancer susceptibility loci (8q24, 17q21, 19p13), but not 2q31. After excluding SNPs from known ovarian cancer susceptibility regions, there were 48 SNPs in 15 regions with $P=5\times10^{-7}$ to 10^{-4}. Five SNPs from four of these loci were genotyped in additional stage 3 samples (2,204 unaffected, 442 with ovarian cancer). Three SNPs showed additional evidence of association with ovarian cancer risk (P<0.02). In the combined stage 1-3 analyses, SNPs rs17631303 and rs183211 (r^2=0.68) on chromosome 17q21.31 had P-values for association of 1×10^{-8} and 3×10^{-8} respectively, and rs4691139 at 4q32.3 had a P-value of 3.4×10^{-8}.

The minor alleles of rs17631303 (HR=1.27, 95%CI:1.17-1.38) and rs183211 (HR=1.25, 95%CI: 1.16-1.35) at 17q21.31 were associated with increased ovarian cancer risk. Analysis of the associations within a competing risks framework, revealed no association with breast cancer risk. The ovarian cancer effect size was maintained but the significance of the association was slightly weaker ($P=2\times10^{-6}$-1×10^{-5}). This is expected because 663 ovarian cancer cases occurring after a primary breast cancer diagnosis were excluded for this analysis. The evidence of association was somewhat stronger under the genotype-specific model (2-df $P=1.6\times10^{-9}$ and $P=2.6\times10^{-9}$ for rs17631303 and rs183211 respectively in all samples combined) with larger HR estimates for the rare homozygote genotypes than those expected under a multiplicative model. Previous studies of the known common ovarian cancer susceptibility alleles found significant associations with ovarian cancer for both *BRCA1* and *BRCA2* carriers. Thus, we evaluated the associations between the 17q21.31 SNPs and ovarian cancer risk for *BRCA2* carriers using iCOGS genotype data (7580 unaffected and 631 affected). Both rs17631303 and rs183211 were associated with ovarian cancer risk for *BRCA2* carriers ($P=1.98\times10^{-4}$ and 9.26×10^{-4}), with similar magnitude and direction of association as for *BRCA1* carriers. Combined analysis of *BRCA1* and *BRCA2* mutation carriers provided strong evidence of association ($P=2.80\times10^{-10}$ and 2.01×10^{-9}).

The combined analysis of stage 1 and 2 samples, and *BRCA2* carriers, identified seven SNPs on the iCOGS array (pairwise r^2 range: 0.68-1.00) from a 1.3Mb (40.8-42.1Mb, build 36.3) region of 17q21.31 that were strongly associated ($P<1.27\times10^{-9}$) with ovarian cancer risk. This large region of strong linkage disequilibrium has previously been identified as a 17q21.31 inversion (~900kb long) consisting of two haplotypes (termed H1 and H2). The minor allele of rs2532348 (MAF=0.21), which tags H2 was associated with increased ovarian cancer risk (Table 4). Stepwise-regression analysis based on observed genotype data retained only one of the seven SNPs in the model, but it was not possible to distinguish between the SNPs. Imputation through the 1000 Genomes Project, revealed several SNPs in 17q21.31 with stronger associations than the most significant genotyped SNP in the combined *BRCA1/2* analysis (rs169201, $P=6.24\times10^{-11}$). The most significant SNP (rs140338099 (17-44034340), $P=3\times10^{-12}$) located in *MAPT*, was highly correlated ($r^2=0.78$) with rs169201 in *NSF*. This locus appears to be distinct from a previously identified ovarian cancer susceptibility locus located >1Mb distal on 17q21 (spanning 43.3-44.3Mb, build 36.3). None of the SNPs in the novel region were strongly correlated with any of the SNPs in the 43.3-44.3Mb region (maximum r^2 =0.07). The most significantly associated SNP from the *BRCA1* GWAS from the 43.3-44.3Mb locus was rs11651753 ($p=4.6\times10^{-4}$) ($r^2<0.023$ with the seven most significant SNPs in the novel 17q21.31 region). An analysis of the joint associations of rs11651753 and rs17631303 from the two 17q21 loci with ovarian cancer risk for *BRCA1* carriers (Stage 1 and 2 samples) revealed that both SNPs remained significant in the model (P-for inclusion=0.001 for rs11651753, 1.2×10^{-6} for rs17631303), further suggesting that the two regions are independently associated with ovarian cancer for *BRCA1* carriers. The 1.3Mb 17q21.31 locus contains 13 genes and several predicted pseudogenes, several of which are expressed in normal ovarian surface epithelium and ovarian adenocarcinoma. Variation in this region has been associated with Parkinson's disease (*MAPT*, *PLEKHM1*, *NSF*, *c17orf69*) progressive supranuclear palsy (*MAPT*), celiac disease (*WNT3*), bone mineral density *(CRHR1*) (NHGRI GWAS catalog) and intracranial volume. Of the top hits for these phenotypes, SNP rs199533 in *NSF*, previously associated with Parkinson's disease and rs9915547 associated with intracranial volume were strongly associated with ovarian cancer ($P<10^{-9}$ in *BRCA1/2* combined). Whether these phenotypes have shared causal variants in this locus remains to be elucidated. Further exploration of the functional relevance of the strongest hits in the 17q21.31 locus ($P<10^{-8}$ in *BRCA1/2* combined) provided evidence that cis-regulatory variation alters expression of several genes at 17q21, including *PLEKHM1, c17orf69, ARHGAP27, WNT3* and *KANSL1*, suggesting that ovarian cancer risk may be associated with altered expression of one or more genes in this region.

The minor allele of rs4691139 at the novel 4q32.3 region was also associated with an increased ovarian cancer risk for *BRCA1* carriers (per-allele HR=1.20, 95%CI:1.17-1.38), but was not associated with breast cancer risk. No other SNPs from the 4q32.3 region on the iCOGS array were more significantly associated with ovarian cancer for *BRCA1* carriers. Analysis of associations with variants identified through 1000 Genomes Project based imputation of the Stage 1 and 2 samples, revealed 19 SNPs with stronger evidence of association ($P=5.4\times10^{-7}$ to 1.1×10^{-6}) than rs4691139. All were highly correlated (pairwise $r^2>0.89$) and the most significant (rs4588418) had $r^2=0.97$ with rs4691139. There was no evidence for association between rs4691139 and ovarian cancer risk for *BRCA2* carriers (HR=1.08, 95%CI: 0.96-1.21, P=0.22). Likewise, no association was found between rs4691139 and ovarian cancer risk in the general population based on data by the Ovarian Cancer Association Consortium (OCAC) in 18,174 cases and 26,134 controls (Odds Ratio=1.00, 95%CI:0.97-1.04, P=0.76). The confidence intervals rule out a comparable effect to that found in *BRCA1* carriers. Therefore, our findings may represent a *BRCA1*-specific association with ovarian cancer risk. The 4q32.2 region contains the several members of the *TRIM* (Tripartite motif containing) gene family, *c4orf39* and *TMEM192*. Of these, only *TRIM60, c4orf39* and *TMEM192* are expressed in normal ovarian epithelium and/or ovarian tumors (TCGA).

Additional genotyping

In the last year we have collected genomic DNA from another 3,000 *BRCA1* mutation carriers. These have just been genotyped on the iCOGS array. The genotype data from stages 1-3 will be combined with these new 3,000 samples (Stage 4) and re-analyzed to identify additional common genetic modifiers of ovarian cancer risk for *BRCA1* mutation carriers.

In summary, we have identified two novel loci associated with ovarian cancer for *BRCA1* mutation carriers that are not associated with breast cancer in *BRCA1* carriers. Of these, the 4q32.2 locus was specifically associated with *BRCA1* ovarian cancer risk, whereas the 17q21.1 locus was associated with ovarian cancer in *BRCA1* and *BRCA2* carriers and the general population. Based on these efforts we have essentially completed Tasks 5 to 9 from Aim 2.

Aim 3: To evaluate risk modifiers from the *BRCA1* breast cancer GWAS and risk factors from sporadic ovarian cancer GWAS as modifiers of ovarian cancer in *BRCA1* carriers.

The next step is to conduct Tasks 10-13. This will involve analysis of all genotype data for all SNPs on the iCOGS array, not just the 35,000 *BRCA1* GWAS SNPs in the stage 1-4 *BRCA1* carrier samples. The array contains many of the known risk factors for breast and ovarian cancer and risk modifiers for breast cancer in *BRCA1* carriers. Specifically, we have identified a total of 74 breast cancer risk loci and 10 ovarian cancer risk loci in the general population, as well as 10 *BRCA1* breast cancer risk modifiers. Variants from these loci on the iCOGS array will be analyzed for associations with *BRCA1* ovarian cancer risk. Those variants not present on the iCOGS array and imputed variants (based on the 1,000 genomes project) from these loci that are not on the iCOGS array will be genotyped on the *BRCA1* carrier DNA samples by custom genotyping approaches and evaluated for associations with ovarian cancer risk in *BRCA1* carriers in months 27-36.

All variants associated with ovarian cancer risk in *BRCA1* carriers will be used to develop risk models for improved age specific ovarian cancer risk assessments for *BRCA1* mutation carriers. For instance, based on the distribution of the seven *BRCA1* ovarian cancer risk modifiers (9p22, 8q24, 3q25, 17q21, 19p13, 17q21.31, and 4q32.3), the 5% of *BRCA1* mutation carriers at lowest risk will have a lifetime risk of developing ovarian cancer of 28% or lower whereas the 5% at highest risk will have a lifetime risk of 63% or higher. Such differences in lifetime or age-specific risks may have practical implications for cancer screening, timing of interventions and family planning for *BRCA1* mutation carriers.

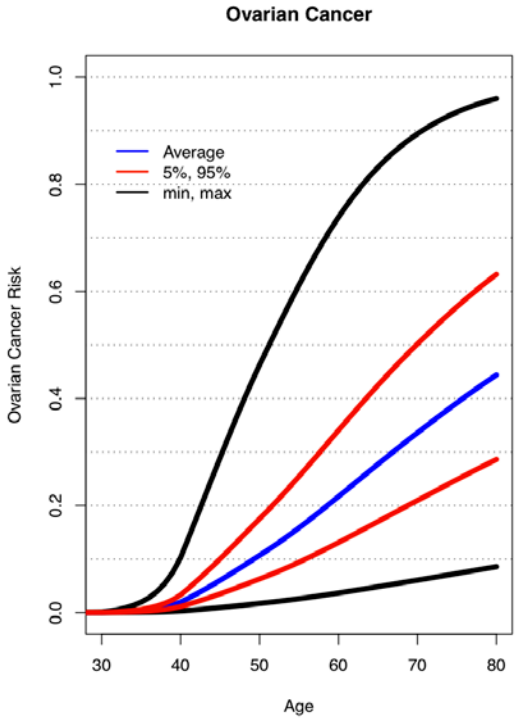

Figure 1: Predicted breast and ovarian cancer risks for *BRCA1* mutation carriers at the 5th and 95th percentiles of the combined SNP profile distributions. The minimum, maximum and average risks are also shown. Predicted cancer risks are based on the associations of known ovarian cancer susceptibility loci (identified through GWAS) with cancer risk for *BRCA1* mutation carriers and loci identified through the present study. Ovarian cancer risks based on the associations with: 9p22, 8q24, 3q25, 17q21, 19p13, 17q21.31, and 4q32.3. Only the top SNP from each region was chosen. Average ovarian cancer risks were obtained from published data.

Key Research Accomplishments

- Completed a validation study of candidate ovarian cancer risk modifiers for *BRCA1* mutation carriers.
- Verified three known ovarian cancer risk factors as ovarian cancer risk modifiers for *BRCA1* mutation carriers
- Identified novel ovarian cancer risk modifier loci for *BRCA1* mutation carriers on chromosome 4q32 and 17q21.

Reportable Outcomes

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Conclusion

In summary, we have completed the discovery and validation phases of an ovarian cancer GWAS for *BRCA1* mutation carriers. We verified that variants from five loci that have been associated with risk of ovarian cancer in the general population are risk modifiers of ovarian cancer for *BRCA1* mutation carriers. In addition, two novel loci at 4q32 and 17q21 were associated with ovarian cancer risk in *BRCA1* carriers. Of these the 4q32 locus was not associated with ovarian cancer in *BRCA2* mutation carriers or the general population. Thus, specific modifiers of ovarian cancer risk exist for this population. The seven establish risk modifiers of ovarian cancer risk were then shown to be useful for predicting differences in individual ovarian cancer risk among *BRCA1* mutation carriers. Ongoing genotyping of other candidate variants are expected to be useful for improved risk assessment of ovarian and breast cancer risk for *BRCA1* and perhaps *BRCA2* mutation carriers. In addition, by identifying the underlying causative variants in these loci we expect to develop a g reater understanding of the initiation factors involved in ovarian cancer.

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Appendices

None.